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## ORIGINAL ARTICLE

# A genome-wide association study for extremely high intelligence

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We used a case–control genome-wide association (GWA) design with cases consisting of 1238 individuals from the top 0.0003 (~170 mean IQ) of the population distribution of intelligence and 8172 unselected population-based controls. The single-nucleotide polymorphism heritability for the extreme IQ trait was 0.33 (0.02), which is the highest so far for a cognitive phenotype, and significant genome-wide genetic correlations of 0.78 were observed with educational attainment and 0.86 with population IQ. Three variants in locus *ADAM12* achieved genome-wide significance, although they did not replicate with published GWA analyses of normal-range IQ or educational attainment. A genome-wide polygenic score constructed from the GWA results accounted for 1.6% of the variance of intelligence in the normal range in an unselected sample of 3414 individuals, which is comparable to the variance explained by GWA studies of intelligence with substantially larger sample sizes. The gene family *plexins*, members of which are mutated in several monogenic neurodevelopmental disorders, was significantly enriched for associations with high IQ. This study shows the utility of extreme trait selection for genetic study of intelligence and suggests that extremely high intelligence is continuous genetically with normal-range intelligence in the population.

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## INTRODUCTION

One of the best-established findings in cognitive science is that individual differences in performance on diverse cognitive tasks correlate about 0.30 and that a general factor explains about 40% of the total variance.<sup>1</sup> This general cognitive ability factor, usually called general intelligence ('g'), is one of the best predictors of important life outcomes including education, occupation, and mental and physical health.<sup>2</sup> General intelligence is also one of the most heritable behavioural traits, with heritability increasing from 40% in childhood to 80% in later adulthood.<sup>3</sup>

Identifying some of the many DNA differences that account for its heritability is key for advancing research in intelligence.<sup>4</sup> Throughout the life sciences, genome-wide association (GWA) studies have been successful in identifying genes associated with complex traits and common disorders. They have also shown that many DNA variants of very small effect size contribute to heritability.<sup>5</sup> Although the small effect size of individual DNA variants detracts from their utility in neurocognitive research, polygenic scores can be created that aggregate the effects of DNA variants to predict genetic propensities for individuals.<sup>6,7</sup> For example, the current strongest polygenic score prediction of a quantitative trait is for height, which predicts nearly 20% of the variance of height in independent samples.<sup>8</sup>

However, these GWA successes in the life sciences have not been reflected in research on intelligence, where relatively few replicated genome-wide significant associations have been found and polygenic scores derived from these GWA studies account for only about 1% of the variance of intelligence.<sup>9–14</sup> Reasons for this

include heterogeneity between measures and samples across studies in meta-analyses and sample sizes that are underpowered for detecting small effect sizes.<sup>15</sup> The major strategy for improving the ability of GWA studies to detect DNA variants of small effect size has been to increase sample size. Empirical support for increasing sample sizes for IQ GWA studies comes from research on years of education, which can be viewed as a proxy measure of intelligence, because it correlates about 0.50 with intelligence.<sup>16</sup> A 2016 GWA study of years of education with 329 000 individuals yielded 74 genome-wide significant hits and a polygenic score accounted for 4% of the variance in independent samples.<sup>17</sup> Even though years of education only correlates 0.50 with intelligence, studies of educational attainment are currently much larger, thus explaining why the polygenic score from the 2016 educational attainment GWA study accounts for ~3.6% of the variance of intelligence,<sup>18</sup> triple the variance in intelligence explained from GWA studies of intelligence itself.

An alternate strategy for increasing power to detect small effects is to study individuals at the extreme of the normal distribution. Intelligence is a normally distributed trait with a positive end of high performance and a problematic end of intellectual disability. The quantitative genetic model proposes that the normal distribution of quantitative traits is caused by many genes of small effect.<sup>19</sup> This implies that extremely high intelligence occurs only if an individual has many of the positive alleles and few of the negative alleles that affect intelligence. For this reason, a large group of individuals of extremely high intelligence should be enriched for alleles associated with

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intelligence and thus yield increased power to detect associations for alleles that operate throughout the normal distribution.<sup>20</sup>

The quantitative genetic model could be construed to suggest that the extreme low end of the distribution of intelligence is the mirror image of the extreme high end; however, new mutations may be drivers of very low IQ, as they can more easily disrupt than improve finely tuned neurocognitive performance. Recent quantitative genetic research supports the hypothesis that extremely high intelligence is caused by the same DNA variants responsible for individual differences in intelligence throughout the normal distribution,<sup>21</sup> whereas extremely low intelligence is caused by DNA variants that are not associated with individual differences in intelligence in the normal distribution.<sup>22</sup>

Here we capitalize on the increased power of association at the high extreme of intelligence as a strategy to facilitate the discovery of alleles that contribute to genetic variation in intelligence throughout the distribution. We conducted a case-control GWA analysis with cases consisting of 1238 individuals from the top 0.0003 (mean IQ score ~170) of the population distribution of intelligence<sup>23,24</sup> and 8172 unselected population-based controls.

## MATERIALS AND METHODS

### Participants

Participants were recruited from two separate US studies. The project received ethical approval from the King's College London Research Ethics Committee (reference number PNM/11/12–51) and from the European Research Council Executive Agency (reference number Ares (2012)56321). Informed consent was obtained from all subjects. All methods were performed in accordance with relevant guidelines and regulations.

**High-intelligence cases (TIP).** Individuals with extremely high intelligence were recruited from the Duke University Talent Identification Program (TIP), a non-profit organization established in 1980 and dedicated to identifying and fostering the development of academically gifted children. Individuals were selected from the United States for participation in TIP on the basis of performance on the Scholastic Assessment Test or American College Test taken at age 12 years rather than the usual age of 18 years. A composite that aggregates verbal and mathematics Scholastic Assessment Test and American College Test scores correlated >0.80 with intelligence test scores<sup>25</sup> and it is estimated that the TIP programme recruits from the top 3% of the intelligence distribution.<sup>23–26</sup> For the present study, TIP cases were selected and DNA solicited from the top 1% of these TIP individuals, representing approximately the top 0.03% of the intelligence distribution. Illumina Infinium OmniExpress (Illumina.com) genotypes were available for 1409 white European Caucasian individuals (1238 subjects post quality control (QC), see below and Supplementary Table S1). The TIP sample was 62% male post QC, which is to be expected for a sample of individuals with high IQ.<sup>27</sup> There was no significant difference in intelligence test scores between males and females. This sample was previously used in a case-control analysis of putative functional exonic variants assayed on the Illumina HumanExome BeadChip.<sup>28</sup>

**Unselected controls (Health and Retirement Study).** The controls for this study were from The University of Michigan Health and Retirement Study (<http://hrsonline.isr.umich.edu>), which is a longitudinal panel study that surveyed a representative sample of ~20 000 people in the United States over the age of 50 years every 2 years. Saliva was collected for DNA extraction and genotyping was performed for 12 507 subjects. The genotyping was performed by the NIH Center for Inherited Disease Research using the Illumina Human Omni-2.5 Quad Beadchip, with coverage of 2.5 million single-nucleotide polymorphisms (SNPs). Genotype data were obtained through dbGaP. Matching to TIP and after QC (see below and Supplementary Table S1) genotypes were available for 8185 white Caucasian individuals.

**Extension sample: The Twins Early Development Study.** Twins Early Development Study (TEDS) is a longitudinal UK-based population sample of over 15 000 families with twins born in England and Wales 1994, 1995 and 1996, and identified from birth records.<sup>29</sup> At age 12 years, individuals were assessed on 16 cognitive tests. Individuals with severe recurrent

medical problems or severe perinatal medical problems were excluded, as were individuals whose first language was not English and individuals who reported their ethnicity as other than 'White'. Phenotypic and genotypic data were available for individuals after QC in cognitive tests for *g* and educational achievement. The *g* measure was available at age 12 years as a core four-test composite version, *n*=3414, and an extended 16-test version, *n*=4731, which includes some items that can be regarded as educational achievement measures such as reading. The primary educational achievement phenotype we used in TEDS were the grades achieved in the English General Certificate of School Education at age 16 years, *n*=3584. Full details are given in Supplementary Text.

### Quality control

For the TIP and Health and Retirement Study data, before SNP imputation and genetic association analyses, SNPs were excluded based on standard criteria such as call rate (<98%), minor allele frequency (MAF <0.5%) and Hardy-Weinberg equilibrium test (*P*-value <10<sup>−6</sup>). Further details are given in the Supplementary Text and Supplementary Table S2.

### SNP imputation

Genotype imputation was carried out based on the Haplotype Reference Consortium reference panel (rv1.1) ([www.haplotype-reference-consortium.org](http://www.haplotype-reference-consortium.org)) using PBWT<sup>30</sup> as implemented in the Sanger Imputation Server ([imputation.sanger.ac.uk](http://imputation.sanger.ac.uk)). Post imputation QC was carried out using QCTOOL v2 (see URLs). Further details are given in the Supplementary Text.

### Single SNP association analysis

The single SNP association analysis was performed using a logistic regression for the imputed SNPs with MAF ≥0.01 and imputation info score ≥0.90 using SNPTEST v2.5.2.<sup>31</sup> These conservative MAF and info score thresholds were applied to accommodate the fact that the two cohorts have been genotyped separately. An additive model was used after adjusting for sex and the first 10 principal components to control for population structure.<sup>32</sup> In SNPTEST we used method 'expected' to account for genotype uncertainty of the genotype dosage scores.

### Replication

Lookups were performed of the genome-wide significant SNP-based findings in four published studies. We also investigated replication of published genome-wide significant findings from related traits from these four studies in the TIP sample.

### LD score regression

Linkage disequilibrium (LD) score regression<sup>33</sup> was used to estimate SNP heritability (*h*<sub>SNP</sub><sup>2</sup>) from GWA summary statistics. Estimates of *h*<sub>SNP</sub><sup>2</sup> on the liability scale were assessed with a prevalence estimate of 0.0003. In addition, genetic correlations (*r*<sub>g</sub>) were estimated with several traits from GWA summary statistics, as well as partitioned LD score *h*<sub>SNP</sub><sup>2</sup> to assess enrichment of heritability in SNPs with specific function annotations and tissue-specific genomic annotations, including the central nervous system. For a full description of these procedures, see Supplementary Text.

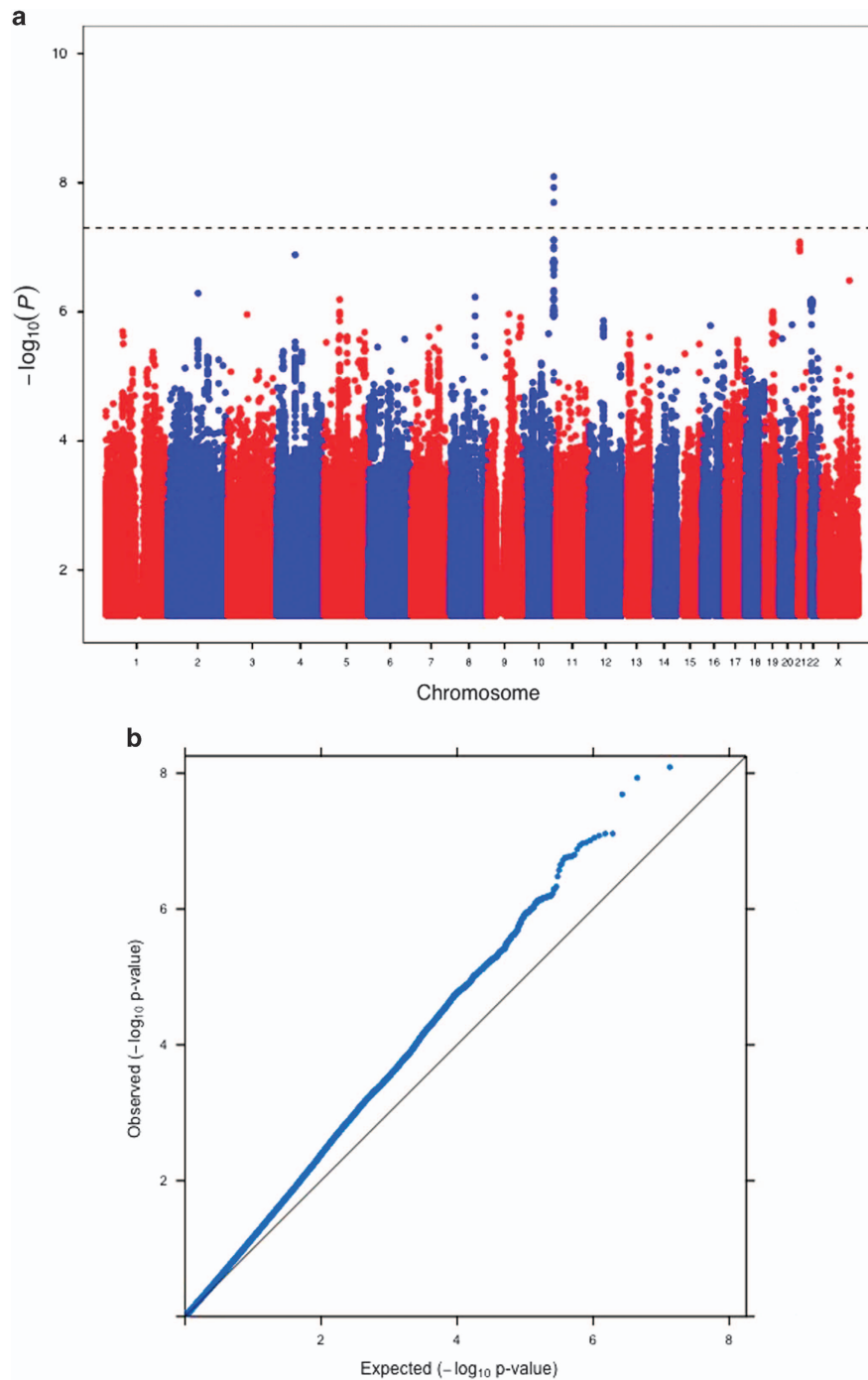
We also used LD score regression to estimate genetic correlations between high intelligence estimated from our TIP GWA analysis with other studies of intelligence and a range of other traits.<sup>33,34</sup> The intent of these comparisons was to evaluate similarities and differences in IQ genetic architecture, to suggest hypotheses about the fundamental genetic basis of intelligence, between very high IQ and IQ in the normal range.

### Gene-based association and pathway analysis

*P*-values quantifying the degree of association of genes and gene-sets in TIP were generated using MAGMA (v1.03).<sup>35</sup> Our approach was guided by rigorous method comparisons of type I error rates of different algorithms.<sup>36,37</sup> Further details are given in Supplementary Text.

### Heritability estimation

We estimated the contribution of all common SNPs (MAF ≥0.01) in this sample by performing a linear mixed-model analysis to fit all genotyped SNPs simultaneously in the model as implemented in GCTA.<sup>38</sup> Heritability



**Figure 1.** Manhattan (a) and Q-Q plot (b) of  $P$ -values of the single-nucleotide polymorphism (SNP)-based association analysis for the case-control status of high IQ. The dotted line indicates the threshold for genome-wide significance ( $P < 5 \times 10^{-8}$ ) for 6 773 587 SNPs adjusted for sex and the first 10 principal components.

was estimated on the liability scale with prevalence = 0.0003 and adjusted for sex and the first 10 PCs for the genotyped SNPs. Heritability was also estimated using the LD score<sup>33</sup> method; estimates were from imputed SNPs and LD was calculated from HapMap 3.

#### Polygenic scores

We used GWA results from TIP to create polygenic scores for the UK-representative TEDS<sup>39</sup> (Supplementary text). Individuals were tested at 12 years and the phenotypes g-4 and g-16 were calculated from 4 and 16 tests at age 12 years, respectively, where the 4 tests are a subset of the 16.

More details about these phenotypes is in Supplementary Text. The two phenotypes were adjusted for age within each testing period and first principal component scores were derived using principal component analysis implemented in R. Imputed genotypes were available for 6710 samples. Stringent QC procedures were applied followed by imputation of SNPs using the Haplotype Reference Consortium reference panel<sup>40</sup> (Supplementary Text). After QC, 7 581 516 genotyped or well-imputed ( $\text{info} > 0.70$ ) variants were available for the polygenic score analyses; 4 657 119 overlapped with variants tested in the independent TIP GWA analysis<sup>17</sup> after exclusions due to nucleotide inconsistencies and  $\text{MAF} < 0.01$ . We created genome-wide polygenic scores for each individual



in the TEDS sample using summary statistics from the TIP GWA analyses and all SNPs. To avoid a reduction in predictive accuracy and loss of information due to pruning markers by LD, we used LDpred,<sup>41</sup> which infers the posterior mean effect size of each marker using a prior based on the proportion of real effects and the distribution of possible effect sizes and reference LD data (we used our sample as the LD reference), and SNPs are weighted accordingly. This was used to assess the association of these polygenic scores with general cognitive ability at age 12 years and educational achievement at the end of compulsory education at age 16 years, using the first 10 principal components as well as genotyping array and plate as covariates to control for population stratification and possible genotyping errors, respectively.

## RESULTS

### Analysis of genome-wide SNPs

After performing the GWA single SNP analysis using an additive model for 6773 587 SNPs, three intronic SNPs: rs4962322, rs4962520 and rs10794073 located in *ADAM12* on chromosome 10 reached genome-wide significant *P*-values of  $8.0 \times 10^{-9}$ ,  $1.2 \times 10^{-8}$  and  $2.0 \times 10^{-8}$ , respectively. The three SNPs are in high LD with  $r^2$  ranging between 0.9 and 1.0, with rs4962322 representing the sentinel SNP after clumping. *ADAM12* encodes a member of the ADAM (a disintegrin and metalloprotease) protein family. Members of this family are membrane-anchored proteins and have been implicated in a variety of biological processes involving cell–cell and cell–matrix interactions, including fertilization, muscle development and neurogenesis (www.ncbi.nlm.nih.gov/gene). Results for all SNPs are presented in Figure 1 and details of the top three SNPs are in Table 1. A regional plot for rs4962322 is shown in Figure 2 and a comparison of the MAF for rs4962322 from the different samples is in Supplementary Table S3.

The genomic inflation  $\lambda$  for these analyses was equal to 1.096 and the LD score intercept is 1.020. This is consistent with inflation largely driven by polygenic variation rather than population stratification.<sup>33</sup> Although there is no similar study in which to carry out replication for the top SNP, we performed a look up of all SNPs with *P*-values  $< 10^{-7}$  including rs4962322 in other studies with similar phenotypes, as described below.

### Replication of single SNP variation

We have performed a look-up of the three top SNPs in four studies with related phenotypes: CHIC<sup>9</sup> (childhood intelligence), CHARGE<sup>11</sup> (normal range adult intelligence), educational attainment<sup>17</sup> and VNR-UKB<sup>12</sup> (numerical and verbal reasoning) (Supplementary Table S4). The direction of effect was concordant with two of the studies for rs4962322 and rs4962520, and only for one study for rs10794073. None of the SNPs replicated in significance. Summary data for rs4962520 were not available for CHIC or CHARGE. We also compared the associations of the four published GWAS with our results; a summary of these is in Supplementary Table S5. There were 95 published genome-wide significant SNPs from the four studies and we found comparable SNP data for 63 of these. Ninety-four percent of the TIP-GWA SNPs

showed concordance in direction of effect with the published SNPs, although none reached genome-wide significance.

### Gene-based association and pathway analyses

To test whether the combined effect of SNPs within a gene has a significant effect, we conducted a gene-based analysis using MAGMA v1.05. The gene with the genome-wide significant marker, *ADAM12*, also ranked first in the gene-based analysis with *P*-value =  $5.82 \times 10^{-6}$  (Bonferroni threshold =  $2.57 \times 10^{-6}$ ). The second top gene, *SH2D1A*, with *P*-value =  $7.66 \times 10^{-6}$ , is located on the X chromosome. Both genes are suggestive but not significant. Top results from the gene-based analyses are in Supplementary Table S6; the full results are in Supplementary Table S7. Pathway analyses were applied to three sets of pathways: gene families, gene intolerance gene sets based on Residual Variation Intolerance Score percentiles and biological pathways. Complete results with links to source data are provided in Supplementary Tables S8–S10 and S10a. Information on gene sets and pathway analysis procedures is given in Supplementary Text. One gene family showed a significant association (*P*-value =  $6.43 \times 10^{-5}$ , Bonferroni threshold =  $1.26 \times 10^{-4}$ ): plexins. Plexins are transmembrane proteins which act as receptors to semaphorins. We also determined the enrichment of intolerant genes in the GWAS by testing gene-sets with decreasing or increasing gene intolerance. The gene intolerance results are given in Supplementary Table S9.

### Heritability and genetic correlation estimation

The proportion of variance explained by all common variants using GCTA was 0.33 (0.02); using LD score regression (with unconstrained intercept), heritability was 0.42 (0.06). These estimates are compatible with a highly polygenic architecture of this extreme IQ trait, given the few genome-wide significant hits we observe. Using LD score regression we also find large and significant genetic correlations between high IQ and other phenotypes from other studies (Table 2). Genetic correlations ranged from 0.75 (0.13) with childhood IQ<sup>9</sup> to 0.86 (0.10) with verbal and numerical reasoning.<sup>12</sup>

We carried out partitioned heritability analysis using LD score regression. The results show that the central nervous system category accounts for the largest proportion of the heritability: 68.8% from 14.8% of SNPs (enrichment *P*-value =  $4.07 \times 10^{-5}$ , Bonferroni threshold =  $8.06 \times 10^{-4}$ ). A summary table with the proportions explained by the 62 categories is in Supplementary Table S11.

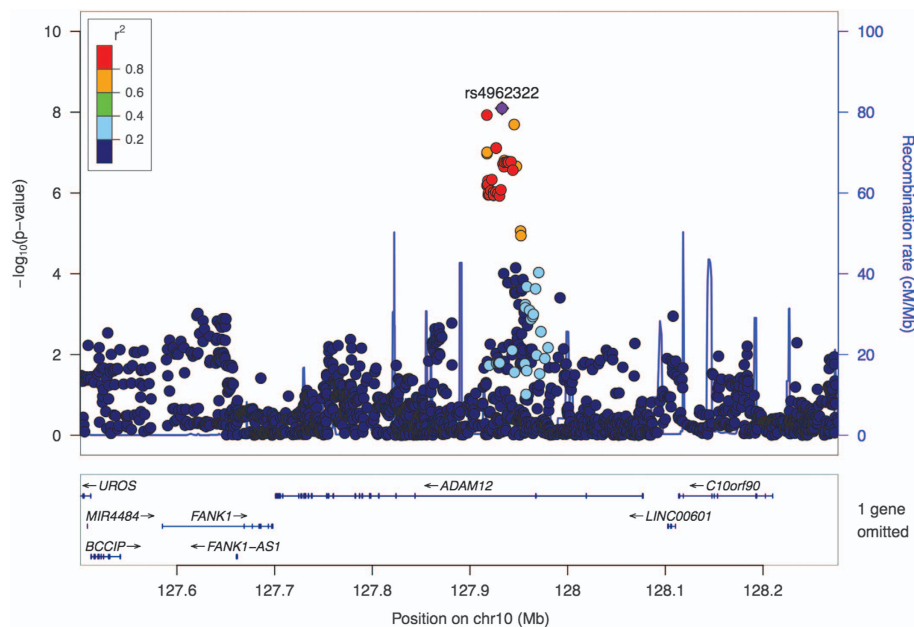
### Polygenic scores

The results from the TIP GWA analyses of extremely high intelligence were used to build polygenic scores in the unselected and representative TEDS sample. Highly significant predictions were observed for individual differences in intelligence ( $r^2 = 2.4\%$  for the broader 16-test composite *g* score at age 12 years and 1.6% for the 4-test composite *g* score at age 12 years. Although the TEDS 16-test composite was better predicted by the polygenic score, this composite includes educationally relevant skills such as

**Table 1.** Genome-wide significant SNPs ( $P < 5 \times 10^{-8}$ ) from the logistic regression

SNP	CHR	BP	OR	s.e.	P-values	A1	A2	MAF	Function	Gene
rs4962322 <sup>a</sup>	10	127 932 765	1.489	0.070	$8.05 \times 10^{-9}$	A	C	0.089	Intronic	ADAM12
rs4962520	10	127 917 302	1.469	0.070	$1.18 \times 10^{-8}$	C	T	0.091	Intronic	ADAM12
rs10794073	10	127 945 261	0.672	0.070	$2.02 \times 10^{-8}$	C	A	0.085	Intronic	ADAM12

Abbreviations: MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism. <sup>a</sup>Sentinel SNP after clumping.



**Figure 2.** Regional plot for single-nucleotide polymorphism (SNP) rs4962322,  $P$ -value =  $2.1 \times 10^{-8}$ .

**Table 2.** Genetic correlations estimated through LD score regression with summary statistics from publicly available data

Phenotype1	Phenotype2	rg	s.e.	P-values
TIP_IQ	Childhood IQ <sup>9</sup>	0.75	0.13	$1.6 \times 10^{-9}$
TIP_IQ	Cognitive performance <sup>11</sup>	0.80	0.08	$3.1 \times 10^{-26}$
TIP_IQ	College completion	0.79	0.08	$2.0 \times 10^{-23}$
TIP_IQ	Years of education	0.79	0.07	$1.9 \times 10^{-26}$
TIP_IQ	VNR-UKB reasoning <sup>12</sup>	0.86	0.10	$1.6 \times 10^{-16}$

Abbreviation: LD, linkage disequilibrium.

reading and mathematics. The TIP-based polygenic score predicted 2.1% of the variance in educational achievement in TEDS (General Certificate of School Education scores at age 16 years), more than explained for intelligence.

## DISCUSSION

We conducted a GWA analysis on the unique TIP sample of highly intelligent individuals selected from the top 0.03% of the intelligence distribution, which reveals that very high IQ is continuous in genetic terms with the normal range of intelligence. We show that polygenic prediction from TIP is stronger than from all current IQ GWAS, only being exceeded by very large studies of the partially correlated phenotype of educational attainment. Our analysis imposed a liability threshold model in which the very high IQ sample were used as cases and compared with a much larger unselected sample of controls. We chose this control group rather than selecting the extreme low end of IQ as controls, because extreme low IQ may be distinct from the rest of the distribution due to the effect of rare mutations such as copy number variants.<sup>22</sup> Strikingly, our data captured a high and significant amount of variation as evident from the estimated SNP heritability of 0.33 (0.02), the highest thus far for GWAS of cognitive abilities.<sup>9,11,12,17</sup>

The high SNP heritability suggested that we had good power to investigate the genetic relationship between high IQ and other phenotypes. Genetic correlations from the TIP GWAS summary statistics calculated with LD score regression were high and

significant for cognitive phenotypes, ranging from 0.75 (0.13) with childhood IQ<sup>9</sup> to 0.86 (0.10) for verbal and numerical reasoning.<sup>12</sup>

In our pathway analysis, the gene family *plexins*, members of which are mutated in several monogenic neurodevelopmental disorders, was significantly enriched for associations with high IQ ( $P$ -value =  $6.43 \times 10^{-5}$ ). The plexin-semaphorin pathway has been linked to axon guidance,<sup>42</sup> mental disability and neural connectivity,<sup>43</sup> axon regeneration in the central nervous system, bone disorders, cancer and inflammatory diseases.<sup>44</sup> Noticeably, the top biological pathway was *GO:SEMAPHORIN\_RECEPTOR\_ACTIVITY* with  $P$ -value =  $5.82 \times 10^{-4}$ ; however, it was not significant. Partitioned LD score analyses also demonstrated a highly significant enrichment of SNP heritability in the central nervous system-annotated portion of the genome—68.8% of the SNP heritability results from 14.8% of SNPs—suggesting a strong role for variation in brain-expressed genes and their regulatory regions.

The primary single-variant findings from our GWA association analysis with high IQ were three intronic SNPs in high LD,  $r^2 \geq 0.90$ : rs4962322 ( $P = 8.05 \times 10^{-9}$ ) and rs4962520 ( $P = 1.18 \times 10^{-8}$ ), and rs10794073 ( $P = 2.02 \times 10^{-8}$ ), all genome-wide significant and located in ADAM12 on chromosome 10. Gene-based analyses also pointed to the same locus, with a gene-wise  $P$ -value =  $5.82 \times 10^{-6}$ . Similar to another study using this same case cohort,<sup>28</sup> there is no available replication cohort with extremely high IQ. Therefore, we compared results from our case-control design to comparable phenotypes in GWA studies of individual differences in the normal range. The three single variants identified in ADAM12 did not replicate in published data for the normal range of intelligence,<sup>11</sup> childhood intelligence,<sup>9</sup> educational attainment,<sup>17</sup> and verbal and numerical reasoning,<sup>12</sup> although the effect was in the same direction in two of the studies for rs4962322 and rs4962520, and only for one study for rs10794073 (Supplementary Table S2). Conversely, lookup of GWA-significant SNPs from these same GWA studies in TIP were likewise not significant (Supplementary Table S5). One possibility is that ADAM12 affects high IQ but not IQ in the normal range.

We also used polygenic scores to test the generalizability of TIP GWA results to individual differences in intelligence and educational achievement. For this, we used TEDS, which is a UK-based study also of white European Caucasian individuals. We used GWA

results from TIP to create polygenic scores, in order to predict variance in normal-range intelligence and educational achievement in TEDS for  $g$  based on four cognitive tests at age 16 years, as well as a broader measure of  $g$  that includes 16 tests, some of which could be considered as assessing educational performance such as reading, mathematics and language. A polygenic score created from the TIP GWA results accounted for 1.6% of the variance in individual differences in intelligence in TEDS at age 16 years for our 4-test composite of intelligence and 2.4% for our 16-test measure of  $g$ .

Focusing on the core 4-test  $g$  measure, we think that accounting for 1.6% of the variance of intelligence is exciting for several reasons. First, this effect size is greater than the effect sizes from previous GWA studies of the normal range of intelligence.<sup>45</sup> The effect size of 1.6% represents > 2.5% of the heritable variance of intelligence, which is comparable to the most robust effect sizes in behavioural research.<sup>46</sup> Second, the result demonstrates that genetic effects on extremely high intelligence are similar to those responsible for the heritability of the normal range of intelligence in the population. That is, extremely high intelligence is quantitatively, not qualitatively, different from the rest of the distribution.<sup>19</sup> Third, it shows the utility of extreme trait ascertainment for genetic analysis of neurocognitive traits as individuals with the extreme (high) phenotype should be enriched for IQ-increasing alleles.

One puzzling finding is that the TIP polygenic score accounts for more variance in educational achievement as assessed by General Certificate of School Education at age 16 (2.1%) years than in intelligence (1.6%). It may be that although the TIP sample has extremely high IQ, individuals were nominated initially by their schools. They were then screened using college entrance examinations, which are a mix of intelligence and educational achievement. For this reason, we speculate that the TIP GWA results represent a mix of intelligence and educational achievement. It may also be the case that additional elements of high IQ are captured by educational achievement.

Although not the focus of this study, we acknowledge the role of the environment, which has been shown to be particularly important in childhood studies of IQ with, conversely, increasing heritability of IQ with age.<sup>47</sup> This work has several limitations. As mentioned previously, there is a lack of a similar replication sample of extremely high IQ individuals to validate our findings. Furthermore, cases and controls were collected separately, which is why our QC protocols were very stringent, resulting in a reduced number of individuals and SNPs. In addition, our case-control design resulted in some loss of power, in contrast to GWA analysis using a quantitative scale. Finally, another limitation is that this study, similar to the other studies mentioned above, is restricted to white Europeans.

In summary, we have shown that extremely high intelligence is a polygenic trait and its high heritability indicates that GWA analysis captures a large portion of the genetic variance. The novel aspect of the present study is that it represents a complementary strategy to the 'brute force' approach of increasing sample sizes of GWA studies of IQ variation in the normal range (and is an example for quantitative trait genetics in general). It demonstrates the utility of a 'positive genetics' strategy of focusing on the extremely high end of the distribution of IQ. Larger scale studies focusing on either high IQ or IQ in the normal range are likely to be successful in the identification of many significant loci and biological pathways.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## URLS

RegulomeDB, <http://regulomedb.org>.

1000 Genomes Project multi-ancestry imputation panel, [https://mathgen.stats.ox.ac.uk/impute/data\\_download\\_1000G\\_phase1\\_integrated.html](https://mathgen.stats.ox.ac.uk/impute/data_download_1000G_phase1_integrated.html). Genotype-based checksums for relatedness determination, [http://www.broadinstitute.org/~sripke/share\\_links/checksums\\_download](http://www.broadinstitute.org/~sripke/share_links/checksums_download). LD-Hub, <http://ldsc.broadinstitute.org> and <https://github.com/mkanai/ggman>

## AUTHOR CONTRIBUTIONS

RP conceived the study. CC, LSH, HP and SN did the genotyping and initial QC. DZ, EK, HG and HMW did the statistical analysis. DZ, GB and RP wrote the manuscript. DZ, EK, HG, CC, LSH, HP, SN, MAS, MP, DL, RP and GB reviewed the manuscript.

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